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PMID: 12975377 [PubMed - indexed for MEDLINE]

2: Jang SB, Won J, Kim H, Kim J, Lee KH, Han H, Rha HK, Choi CR. Related Articles, Links

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3: Wang C, Deng L, Hong M, Akkaraju GR, Inoue J, Chen ZJ. Related Articles, Links

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Nature. 2001 Jul 19;412(6844):346-51.
PMID: 11460167 [PubMed - indexed for MEDLINE]

4: Holtmann H, Enninga J, Kalble S, Thiefes A, Dorrie A, Broemer M, Winzen R, Wilhelm A, Ninomiya-Tsuji J, Matsumoto K, Resch K, Kracht M. Related Articles, Links

The MAPK kinase kinase TAK1 plays a central role in coupling the interleukin-1 receptor to both transcriptional and RNA-targeted mechanisms of gene regulation.
J Biol Chem. 2001 Feb 2;276(5):3508-16. Epub 2000 Oct 24.
PMID: 11050078 [PubMed - indexed for MEDLINE]

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L5 ANSWER 1 OF 12 MEDLINE on STN DUPLICATE 1
AN 2005104514 IN-PROCESS
DN PubMed ID: 15725700
TI Nuclear receptors as targets for drug development: crosstalk between
peroxisome proliferator-activated receptor gamma and **cytokines** in bone marrow-derived mesenchymal stem cells.
AU Takada Ichiro; Suzawa Miyuki; Kato Shigeaki
CS Institute of Molecular and Cellular Bioscience, University of Tokyo,
Japan.. itakada@iam.u-tokyo.ac.jp
SO Journal of pharmacological sciences, (2005 Feb) 97 (2) 184-9. Electronic
Publication: 2005-02-11.
Journal code: 101167001. ISSN: 1347-8613.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20050301
Last Updated on STN: 20050316
AB Peroxisome proliferator-activated receptor gamma (PPARgamma) is a ligand-dependent nuclear receptor and regulates adipogenesis and fat
metabolism. PPARgamma is activated by fatty acid derivatives and some
synthetic compounds such as the thiazolidinediones. In addition, certain

cytokines were known to affect the transactivation function of PPARgamma. However, the molecular mechanism of the functional interaction between PPARgamma and **cytokine** signaling remains unclear. We found that combined treatment of PPARgamma and **cytokines** (**IL-1** or TNF-alpha) inhibited adipogenesis and induced osteoblastgenesis in bone marrow-derived mesenchymal stem cells. Furthermore, we showed that the ligand dependent transactivation function of PPARgamma was suppressed by **IL-1** and TNF-alpha. This suppression was mediated through NF-kappaB activated by the **TAK1**/**TAB1**-NIK cascade, a downstream cascade triggered with **IL-1** or TNF-alpha signaling. Thus, we have identified a molecular mechanism of functional cross-talk between PPARgamma and **cytokine** signaling that may provide a theoretical basis for development of novel therapeutical strategies and design of novel compounds for treatment of obesity, diabetes, and some other chronic diseases.

L5 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:360779 CAPLUS
DN 138:380400
TI **TAK1**-**TAB1** fusion protein: a novel constitutively active mitogen-activated protein kinase kinase kinase for use in drug screening
IN Sugita, Naohisa; Sakurai, Hiroaki; Sato, Naoya
PA Tanabe Seiyaku Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 34 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003135070	A2	20030513	JP 2001-335988	20011101

PRAI JP 2001-335988 20011101

AB A fusion protein comprising human transforming growth factor-β-activated kinase 1 (TAK1) N-terminal MAPKKK domain and human **TAK1** binding protein 1 (**TAB1**) C-terminal **TAK1** activation domain, functional as active mutant TAK1, encoding cDNAs, recombinant expression, and use in screening TAK1 inhibitors, are disclosed. **TAK1** and **TAB1** are connect via a linker peptide. Activation of JNK, p38, or IKK, or induction of **cytokine** production, such as IL-6, **IL-1**, or TNF, may be assayed for

screening. TAK1 mitogen-activated protein kinase kinase kinase (MAP3K) is activated by its specific activator, **TAK1**-binding protein 1 (**TAB1**). A constitutively active TAK1 mutant has not yet been generated due to the indispensable requirement of **TAB1** for **TAK1** kinase activity. In this study, the authors generated a novel constitutively active TAK1 by fusing its kinase domain to the minimal **TAK1**-activation domain of **TAB1**. Co-immunopptn. assay demonstrated that these domains interacted intra-molecularly. The **TAK1-TAB1** fusion protein showed a significant MAP3K activity in vitro and activated c-Jun N-terminal kinase/p38 MAPKs and IκB kinase in vivo, which was followed by increased production of interleukin-6. These results indicate that the fusion protein is useful for characterizing the physiol. roles of the **TAK1-TAB1** complex.

L5 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:883731 CAPLUS
DN 139:394860
TI Feedback control of the protein kinase TAK1 by SAPK2a/p38α
AU Cheung, Peter C. F.; Campbell, David G.; Nebreda, Angel R.; Cohen, Philip
CS MSI/WTB Complex, School of Life Sciences, MRC Protein Phosphorylation Unit, University of Dundee, Dundee, DD1 5EH, UK
SO EMBO Journal (2003), 22(21), 5793-5805
CODEN: EMJODG; ISSN: 0261-4189
PB Oxford University Press
DT Journal
LA English
AB TAB1, a subunit of the kinase TAK1, was phosphorylated by SAPK2a/p38α at Ser423, Thr431 and Ser438 in vitro. TAB1 became phosphorylated at all three sites when cells were exposed to cellular stresses, or stimulated with tumor necrosis factor-α (TNF-α), interleukin-1 (**IL-1**) or **lipopolysaccharide** (**LPS**). The phosphorylation of Ser423 and Thr431 was prevented if cells were pre-incubated with SB 203580, while the phosphorylation of Ser438 was partially inhibited by PD 184352. Ser423 is the first residue phosphorylated by SAPK2a/p38α that is not followed by proline. The activation of TAK1 was enhanced by SB 203580 in **LPS**-stimulated macrophages, and by proinflammatory **cytokines** or osmotic shock in epithelial KB cells or embryonic fibroblasts. The activation of TAK1 by TNF-α, **IL-1** or osmotic shock was also enhanced in embryonic fibroblasts from SAPK2a/p38α-deficient mice,

while incubation of these cells with SB 203580 had no effect. Our results
suggest that TAB1 participates in a SAPK2a/p38α-mediated feedback
control of TAK1, which not only limits the activation of SAPK2a/p38α
but synchronizes its activity with other signalling pathways that lie
downstream of TAK1 (JNK and IKK).
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:118999 CAPLUS
DN 139:33778
TI TAB2 is essential for prevention of apoptosis in fetal liver but not for
interleukin-1 signaling
AU Sanjo, Hideki; Takeda, Kiyoshi; Tsujimura, Tohru; Ninomiya-Tsuji, Jun;
Matsumoto, Kunihiro; Akira, Shizuo
CS Department of Host Defense, Research Institute for Microbial Diseases,
Osaka University, Osaka, 565-0871, Japan
SO Molecular and Cellular Biology (2003), 23(4), 1231-1238
CODEN: MCEBD4; ISSN: 0270-7306
PB American Society for Microbiology
DT Journal
LA English
AB The proinflammatory **cytokine** interleukin-1 (**IL-1**) transmits a signal via several critical cytoplasmic proteins such
as MyD88, IRAKs and TRAF6. Recently, serine/threonine kinase TAK1 and
TAK1 binding protein 1 and 2 (TAB1/2) have been identified as mols.
involved in **IL-1**-induced TRAF6-mediated activation of
AP-1 and NF-κB via mitogen-activated protein (MAP) kinases and
IκB kinases, resp. However, their physiol. functions remain to be
clarified. To elucidate their roles in vivo, we generated TAB2-deficient
mice. The TAB2 deficiency was embryonic lethal due to liver degeneration
and apoptosis. This phenotype was similar to that of NF-κB p65-,
IKKβ-, and NEMO/IKKγ-deficient mice. However, the **IL-1**-induced activation of NF-κB and MAP kinases was not
impaired in TAB2-deficient embryonic fibroblasts. These findings
demonstrate that TAB2 is essential for embryonic development through
prevention of liver apoptosis but not for the **IL-1**

receptor-mediated signaling pathway.
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 12 MEDLINE on STN DUPLICATE 2
AN 2003132605 MEDLINE
DN PubMed ID: 12598905
TI **Cytokines** suppress adipogenesis and PPAR-gamma function through the **TAK1/TAB1**/NIK cascade.
AU Suzawa Miyuki; Takada Ichiro; Yanagisawa Junn; Ohtake Fumiaki; Ogawa Satoko; Yamauchi Toshimasa; Kadowaki Takashi; Takeuchi Yasuhiro; Shibuya Hiroshi; Gotoh Yukiko; Matsumoto Kunihiro; Kato Shigeaki
CS Institute of Molecular and Cellular Biosciences, University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan.
SO Nature cell biology, (2003 Mar) 5 (3) 224-30.
Journal code: 100890575. ISSN: 1465-7392.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200304
ED Entered STN: 20030321
Last Updated on STN: 20030422
Entered Medline: 20030421
AB Pluripotent mesenchymal stem cells in bone marrow differentiate into adipocytes, osteoblasts and other cells. Balanced cytodifferentiation of stem cells is essential for the formation and maintenance of bone marrow; however, the mechanisms that control this balance remain largely unknown. Whereas **cytokines** such as interleukin-1 (**IL-1**) and tumour-necrosis factor-alpha (TNF-alpha) inhibit adipogenesis, the ligand-induced transcription factor peroxisome proliferator-activated receptor-gamma (PPAR-gamma), is a key inducer of adipogenesis. Therefore, regulatory coupling between **cytokine**- and PPAR-gamma-mediated signals might occur during adipogenesis. Here we show that the ligand-induced transactivation function of PPAR-gamma is suppressed by **IL-1** and TNF-alpha, and that this suppression is mediated through NF-kappaB activated by the **TAK1/TAB1** /NF-kappaB-inducing kinase (NIK) cascade, a downstream cascade associated with **IL-1** and TNF-alpha signalling. Unlike suppression of the PPAR-gamma transactivation function by

mitogen-activated protein kinase-induced growth factor signalling through phosphorylation of the A/B domain, NF-kappaB blocks PPAR-gamma binding to DNA by forming a complex with PPAR-gamma and its AF-1-specific co-activator PGC-2. Our results suggest that expression of **IL-1** and TNF-alpha in bone marrow may alter the fate of pluripotent mesenchymal stem cells, directing cellular differentiation towards osteoblasts rather than adipocytes by suppressing PPAR-gamma function through NF-kappaB activated by the **TAK1**/**TAB1**/NIK cascade.

L5 ANSWER 6 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:568462 BIOSIS
DN PREV200300563327
TI SALMONELLA FLAGELLIN ACTIVATES A NOVEL GP91-PHOX ISOFORM (NOX1) EXPRESSED IN COLONIC EPITHELIAL CELLS.
AU Rokutan, Kazuhito [Reprint Author]; Kuwano, Yuki; Kawahara, Tsukasa; Kodama, Nanae; Kondo-Teshima, Shigetada; Nakamura, Keiya
CS Tokushima, Tokushima, Japan
SO Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. T1092. e-file.
Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003.
American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Dec 2003
Last Updated on STN: 3 Dec 2003
AB BACKGROUNDS/AIMS: Reactive oxygen species (ROS) regulate a variety of biological processes. During the last two years, the cDNAs for six new homologs of human gp91-phox have been cloned: NADPH oxidase (Nox)/dual oxidase (Duox) family. Among the Nox/Duox family, Nox1 is predominantly expressed in the human colon, while its pathophysiological roles are not fully understood. We report here that the colonic Nox1 is sensitive to Salmonella flagellin and increases superoxide generation possibly through

the TLR5 signaling. MATERIAL AND METHODS: Primary cultures of guinea pig large intestinal epithelial cells and human cancer cell lines (Caco2, T84, and HT29 cells) were used in this study. Expression of the Nox/Duox isozyme transcripts were examined by RT-PCR, and all of the isozyme proteins and the cytosolic components of phagocyte NADPH oxidase (p22-phox, p67-phox, p47-phox, p40-phox, and rac1/2) were measured by immunoblot analysis with specific antibodies against the respective proteins. Transduction of p67-phox, p47-phox, and dominant negative MyD88 was performed using respective adenovirus vectors. RESULTS: The primary cultures secreted large amounts of superoxide (150 nmol/mg protein/h), while the cell lines produced small amounts (2-3 nmol/mg protein/h). Among the Nox/Duox family, only Nox1 isoform was expressed in the colonic epithelial cells tested. Primary cultured cells also expressed p22-phox, p67-phox, and rac1, but cancer cell lines possessed p22-phox and rac1. Overexpression of p67-phox failed to increase superoxide generation in Caco2 cells, but co-transfection of p67-phox and p47-phox up-regulated the production 10-fold. None of **cytokines** (**IL-1** -beta, TNF-alpha, and IFN-gamma), growth factors (EGF and TGF-beta), E. coli **LPS**, and PMA up-regulated the Nox1 activity. Salmonella flagellin (FliC) stimulated constitutively expressed TLR5 in Caco2 cells, phosphorylated **TAK1**/**TAB1**, and increased superoxide production 2-fold. This up-regulation was cancelled by dominant negative MyD88. DISCUSSION: Our results show that the cytosolic components (p67-phox and/or p47-phox) are required for full activation of the potent Nox1 expressed in colonic epithelial cells. Nox1 expressed on surface mucous cells of the colon may play an important role in host epithelial cell-bacterial interactions for host defense.

L5 ANSWER 7 OF 12 BIOSIS

AN 2004:193972 BIOSIS
DN PREV200400194532
TI TAK1 - mediated induction of nitric oxide synthase and **cytokine** gene expression in glial cells.
AU White, S. [Reprint Author]; Shen, Q. [Reprint Author]; Fan, F. [Reprint Author]; Griesemer, D. [Reprint Author]; Bhat, N. R. [Reprint Author]
CS Neurol., Med. Univ. of South Carolina, Charleston, SC, USA
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 103.12. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004
AB Inflammatory cell signaling leading to transcriptional activation is primarily mediated by signal transduction via mitogen-activated protein kinase (MAPK) and NFKAPPAB pathways. A common upstream kinase that signals the activation of these pathways is TGFbeta-activated kinase1 (TAK1), which itself becomes activated in response to **cytokines** and upon engagement of a class of cell surface receptors involved in innate immunity i.e., Toll-like receptors (TLRs) by bacterial and viral pathogens. This study directly tests the role of TAK1 in the induction of inducible nitric oxide (NO) synthase (iNOS) and **cytokines** in glial cells, the immune-regulatory cells of the CNS, by transient transfection assays. Transfection of C-6 glia and a rat microglial cell line with TAK1 (but not its inactive form) along with its activator protein i.e., **TAK1**-binding protein 1 (**TAB1**) resulted in a marked stimulation of a co-transfected rat iNOS promoter-reporter construct (iNOS-Luc). TAK1-induced iNOS-Luc activity was substantially inhibited by pharmacological inhibitors of the known down-stream kinases i.e., p38 MAPK and JNK (i.e., SB203580 and SP620125) and was almost completely blocked by co-expression of a phosphorylation mutant of

IKAPPAB. **TAK1/TAB1** also induced the production of NO and the expression of iNOS and the **cytokine** i.e., IL-1beta in microglial cells in a p38 MAPK-, JNK-and NFKAPPAB-dependent manner. The results of these studies provide evidence for an important role for TAK1-mediated intracellular signaling, via p38 MAPK, JNK and NFKAPPAB, in the transcriptional activation of iNOS and **cytokine** genes in glial cells.

L5 ANSWER 8 OF 12 MEDLINE on STN DUPLICATE 3
AN 2001269992 MEDLINE
DN PubMed ID: 11050078
TI The MAPK kinase kinase TAK1 plays a central role in coupling the interleukin-1 receptor to both transcriptional and RNA-targeted mechanisms of gene regulation.
AU Holtmann H; Enninga J; Kalble S; Thiefes A; Dorrie A; Broemer M; Winzen R; Wilhelm A; Ninomiya-Tsuji J; Matsumoto K; Resch K; Kracht M
CS Institute of Pharmacology, Medical School Hannover, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany.
SO Journal of biological chemistry, (2001 Feb 2) 276 (5) 3508-16. Electronic Publication: 2000-10-24.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200106
ED Entered STN: 20010625
Last Updated on STN: 20030105
Entered Medline: 20010621
AB Mechanisms of fulminant gene induction during an inflammatory response were investigated using expression of the chemoattractant cytokine interleukin-8 (IL-8) as a model. Recently we found that coordinate activation of NF-kappaB and c-Jun N-terminal protein kinase (JNK) is required for strong IL-8 transcription, whereas the p38 MAP kinase (MAPK) pathway stabilizes the IL-8 mRNA. It is unclear how these pathways are coupled to the receptor for **IL-1**, an important physiological inducer of IL-8. Expression of the MAP kinase kinase kinase (MAPKKK) **TAK1** together with its coactivator **TAB1** in

HeLa cells activated all three pathways and was sufficient to induce IL-8 formation, NF-kappaB + JNK2-mediated transcription from a minimal IL-8 promoter, and p38 MAPK-mediated stabilization of a reporter mRNA containing IL-8-derived regulatory mRNA sequences. Expression of a kinase-inactive mutant of TAK1 largely blocked **IL-1** -induced transcription and mRNA stabilization, as well as formation of endogenous IL-8. Truncated **TAB1**, lacking the **TAK1** binding domain, or a TAK1-derived peptide containing a TAK1 autoinhibitory domain were also efficient in inhibition. These data indicate that the previously described three-pathway model of IL-8 induction is operative in response to a physiological stimulus, **IL-1**, and that the MAPKKK TAK1 couples the **IL-1** receptor to both transcriptional and RNA-targeted mechanisms mediated by the three pathways.

L5 ANSWER 9 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2002:4979 BIOSIS
DN PREV200200004979
TI Inhibition of adipogenesis by **cytokines** with suppression of PPARgamma function through **TAK1**/**TAB1**-NIK promotes osteoblastogenesis.
AU Suzawa, M. [Reprint author]; Takada, I. [Reprint author]; Yanagisawa, J. [Reprint author]; Takeuchi, Y.; Goroh, Y. [Reprint author]; Matsumoto, K.; Kato, S. [Reprint author]
CS IMBC, University of Tokyo/CREST, Tokyo, Japan
SO Journal of Bone and Mineral Research, (September, 2001) Vol. 16, No. Suppl. 1, pp. S496. print.
Meeting Info.: Twenty-Third Annual Meeting of the American Society for Bone and Mineral Research. Phoenix, Arizona, USA. October 12-16, 2001.
CODEN: JBMREJ. ISSN: 0884-0431.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 28 Dec 2001
Last Updated on STN: 25 Feb 2002

L5 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:278128 CAPLUS
DN 132:320956

TI Method for screening compound inhibiting signal transduction of inflammatory **cytokine**

IN Tsuchiya, Masayuki; Ohtomo, Toshihiko; Sugamata, Yasuhiro; Matsumoto, Kunihiro

PA Chugai Seiyaku K. K., Japan

SO PCT Int. Appl., 100 pp.
CODEN: PIXXD2

DT Patent

LA Japanese

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000023610	A1	20000427	WO 1999-JP5817	19991021
AU 9962278	A1	20000508	AU 1999-62278	19991021
EP 1127944	A1	20010829	EP 1999-949347	19991021

PI WO 2000023610 A1 20000427 WO 1999-JP5817 19991021

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AU 9962278 A1 20000508 AU 1999-62278 19991021

EP 1127944 A1 20010829 EP 1999-949347 19991021

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRAI JP 1998-299962 A 19981021

WO 1999-JP5817 W 19991021

AB By inhibiting the signal transduction of TAK1, effects of inflammatory **cytokines** are depressed, the production of inflammatory **cytokines** (**IL-1**, TNF, etc.) induced by inflammatory stimulus is depressed and the production of other inflammatory **cytokines** (IL-6, etc.) induced by the inflammatory **cytokines** is depressed. The assay comprises contacting **TAK1** and **TAB1** (**TAK1** kinase binding protein 1) with the sample, monitoring formation of **TAK1** kinase-

TAB1 complexes, and screening compound that inhibits **TAK1**-**TAB1** binding. The method may also use labeled anti-TAB1 antibody for drug screening.
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 12 MEDLINE on STN DUPLICATE 4
AN 2000167218 MEDLINE
DN PubMed ID: 10702308
TI TAK1 mitogen-activated protein kinase kinase kinase is activated by
autophosphorylation within its activation loop.
AU Kishimoto K; Matsumoto K; Ninomiya-Tsuji J
CS Department of Molecular Biology, Graduate School of Science, Nagoya
University and CREST, Japan Science and Technology Corporation, Chikusa-ku, Nagoya 464-8602, Japan.
SO Journal of biological chemistry, (2000 Mar 10) 275 (10) 7359-64.

Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200004
ED Entered STN: 20000413
Last Updated on STN: 20000413
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AB TAK1, a member of the mitogen-activated kinase kinase kinase family, is
activated in vivo by various **cytokines**, including interleukin-1 (**IL-1**), or when ectopically expressed together with the **TAK1**-binding protein **TAB1**. However, this molecular mechanism of activation is not yet understood. We show here that endogenous **TAK1** is constitutively associated with **TAB1** and phosphorylated following **IL-1** stimulation. Furthermore, TAK1 is constitutively phosphorylated when ectopically overexpressed with TAB1. In both cases, dephosphorylation of TAK1 renders it inactive, but it can be reactivated by preincubation with ATP. A mutant of TAK1 that lacks kinase activity is not phosphorylated either following **IL-1** treatment or when coexpressed with **TAB1**, indicating that **TAK1** phosphorylation is due to autophosphorylation. Furthermore, mutation to alanine of a conserved serine residue (Ser-192) in the activation loop between kinase domains VII and VIII abolishes both phosphorylation and activation of TAK1. These

results suggest that **IL-1** and ectopic expression of **TAB1** both activate **TAK1** via autophosphorylation of Ser-192.

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TI Functional analysis of apoptosis signal-regulating kinase 1 (ASK 1)-binding proteins
AU Mochida, Yoshiyuki
CS Maxillofacial Surg., Maxillofacial Reconstruction Function., Div. Maxillofacial Neck Reconstruction, Grad. Sch., Tokyo Med. Dent. Univ., Japan
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AB Tumor necrosis factor (TNF) and interleukin-1 (**IL-1**) are pleiotropic **cytokines** that activate two transcription factors, Activator Protein-1 (AP-1) and Nuclear Factor-κB (NF-κB). Apoptosis signal-regulating kinase 1 (ASK 1) is a mitogen-activated protein (MAP) kinase kinase kinase (MAPKKK) that is activated by TNF and **IL-1**, and stimulates c-Jun N-terminal kinase (JNK also known as SAPK; stress-activated protein kinase) and p38 activation. Through genetic screening for ASK 1-binding proteins, Transforming Growth Factor β (TGF-β)-activated kinase (TAK1), another MAPKKK family protein, was identified. Here we report that ASK 1 binds to TAK 1 and dissocs. TAK 1 from TNF receptor-associated factor 6 (TRAF 6), and inhibits TAK 1- and TRAF 6-, but not NFκB-inducing kinase (NIK)-induced NF-κB activation.

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